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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/670,488

09/24/2003

Edward Roydon Jost-Price

50164/026004

8006

21559

7590

09/04/2008

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BOSTON, MA 02110

EXAMINER

JAVANMARD, SAHAR

ART UNIT

PAPER NUMBER

1617

NOTIFICATION DATE

DELIVERY MODE

09/04/2008

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/670,488	<b>Applicant(s)</b> JOST-PRICE ET AL.	
	<b>Examiner</b> SAHAR JAVANMARD	<b>Art Unit</b> 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 14 April 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-41, 46-53, 58-70 and 73-75 is/are pending in the application.
- 4a) Of the above claim(s) 22-41, 49-53 and 70 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-21, 46-48, 58-69 and 73-76 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                        |                                                                   |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/3/07; 6/9/08</u>                                           | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of the Application***

This Office Action is in response to applicant's arguments filed on 04/14/2008. Claim(s) 1-41, 46-53, 58-70, and 73-75 are pending. Claims 22-41, 49-53 and 70, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. Claim(s) 1-21, 46-48, 58-69, and 73-76 are examined herein.

### ***Response to Arguments***

With respect to the double patenting rejection of claims 1-21, Applicants wish to hold this rejection in abeyance until indications of allowable subject matter in this application have been received, thus the rejection is hereby maintained.

Applicant's arguments with respect to the 103(a) obviousness rejection of claims 1-8, 10-18, 15, 20, 21, 46-48, 58, 59, 62-69, and 73-76 as being unpatentable over Siegel et al. (US Patent No. 6,204,245 B1) has been fully considered but found not persuasive. The 103(a) obviousness rejection of the last Office Action has been maintained for reasons of record. The rejection is reiterated below for Applicant's convenience.

With respect to this rejection, Applicant's argue that "...the Office has failed to provide a reason why one skilled in the art would choose the combination of an SSRI and a glucocorticoid from the 406 different combinations ( $14 \times 29 = 406$ ) disclosed by Siegel, and, for this reason, a *prima facie* case of obviousness has not been made."

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Examiner respectfully notes that even though there are many SSRIs and glucocorticoids, all are well known in the art and it would be well within the skill of the artisan to attempt with a reasonable degree of success the formulation of Applicant's compositions. Further, Applicant's themselves have listed an assortment of SSRIs and glucocorticoids in their claimed invention.

Applicant further argues that the combinations of their invention demonstrate synergism. This is not persuasive because synergism is not commensurate in scope with the claimed invention.

Applicant's arguments with respect to the 103(a) obviousness rejection of claims 13, 14, 16-18, 64, 65, and 67-69 over Siegel in view of Linden, Guenther, and Mitra has been fully considered but found not persuasive. The 103(a) obviousness rejection of the last Office Action has been maintained for reasons of record. The rejection is reiterated below for Applicant's convenience.

Applicant argues that "...Siegel is directed to compositions and methods for the treatment of narcolepsy and cataplexy. Linden, Guenther, and Mitra are each directed to the treatment of psoriasis. The Office provides no reasoning as to why one would combine the teachings of Siegel with those of Linden, Guenther, and Mitra."

Examiner respectfully notes that although Siegel does not specifically teach psoriasis, Siegel teaches the combination of corticosteroids and cyclosporin (see page 8, Office Action mailed 10/11/20076). Linden teaches that first line treatments for psoriasis include corticosteroids and cyclosporin (see page 15, Office Action mailed 10/11/20076). Thus it would have been obvious to one of ordinary skill in the art at the

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time of the invention that in addition to treating narcolepsy and catalepsy as taught in Siegel, psoriasis would also be an ailment that would be treated. Thus it is very proper in fact to combine the teachings of Siegel with those of Linden, Guenther, and Mitra as they are all directed to the same purpose.

Furthermore, the reason or motivation to modify a reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. While there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention (MPEP 2144).

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal

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disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 of copending Application No. 10/947455. Although the conflicting claims are not identical, they are not patentably distinct from each other because

Claim 1 of the present application is drawn to a composition comprising a selective serotonin reuptake inhibitor (SSRI) and a corticosteroid. Claim 2 of the present application further limits the SSRI as being selected from a variety of SSRIs (including paroxetine and fluoxetine). Claim 3 of the present application further limits the corticosteroid as being selected from a variety of corticosteroids (including prednisolone, prednisone and hydrocortisone). Claim 46 of the present application is drawn to a composition comprising an SSRI and a glucocorticoid receptor modulator. Claim 58 of the present application is drawn to a pharmaceutical composition comprising an SSRI and a second compound selected from the group consisting of a xanthine, anticholinergic compound, beta receptor agonist, bronchodilator, NSAID, DMARD, COX-2 inhibitor, non-steroidal calcineurin inhibitor, vitamin D analog, psoralen, retinoid and 5-amino salicylic acid. Claim 73 of the present application is drawn to a kit comprising a composition comprising a SSRI and a corticosteroid and instructions.

Claim 1 of the '455 application is drawn to a composition comprising a SSRI, or

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analog thereof, and a corticosteroid.

The claims overlap in scope with nearly identical language with exception of the '455's "analog thereof".

Claims 1-21 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24, 51-54, 66-80 and 82-85 of copending Application No. 10/777517. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claim 1 of the present application is drawn to a composition comprising a selective serotonin reuptake inhibitor (SSRI) and a corticosteroid. Claim 2 of the present application further limits the SSRI as being selected from a variety of SSRIs (including paroxetine and fluoxetine). Claim 3 of the present application further limits the corticosteroid as being selected from a variety of corticosteroids (including prednisolone, prednisone and hydrocortisone). Claim 46 of the present application is drawn to a composition comprising an SSRI and a glucocorticoid receptor modulator. Claim 58 of the present application is drawn to a pharmaceutical composition comprising an SSRI and a second compound selected from the group consisting of a xanthine, anticholinergic compound, beta receptor agonist, bronchodilator, NSAID, DMARD, COX-2 inhibitor, non-steroidal calcineurin inhibitor, vitamin D analog, psoralen, retinoid and 5-amino salicylic acid. Claim 73 of the present application is drawn to a kit comprising a composition comprising a SSRI and a corticosteroid and instructions.

Claim 1 of the '517 application is drawn to a composition comprising a SSRI, or

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analog thereof, and a corticosteroid.

Claim 2 of the '517 application further limits the SSRI as being selected from a variety of SSRIs (including paroxetine and fluoxetine). Claim 3 of the '517 application further limits the corticosteroid as being selected from a variety of corticosteroids (including prednisolone, prednisone and hydrocortisone). Claim 51 of the '517 application is drawn to a composition comprising an SSRI and a glucocorticoid receptor 'modulator. Claim 66 of the '517 application is drawn to a pharmaceutical composition comprising an SSRI and a second compound selected from the group consisting of a xanthine, anticholinergic compound, beta receptor agonist, bronchodilator, NSAID, DMARD, COX-2 inhibitor, non-steroidal calcineurin inhibitor, vitamin D analog, psoralen, retinoid and 5-amino salicylic acid. Claim 82 of the '517 application is drawn to a kit comprising a composition comprising a SSRI or SNRI and a corticosteroid and instructions.

The '517 application differs only in that a SNRI may be utilized as well as a SSRI. The fact that both the '517 and present application utilize open claim language claim 1 of the present application clearly obviates the inclusion of a SNRI compound.

These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:



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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11-12, 15, 20-21, 46-48, 58-59, 60-63, 66, and 73-76 rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al. (US Patent No. 6204245B1).

Siegel et al. teach, in col. 3 line 49 to col. 4 line 27, "...one treatment regime entails administering at least one immunosuppressive agent selected from the group consisting of a nonsteroidal anti-inflammatory drug, a glucocorticoid, hydroxychloroquine, sulfasalazine, methotrexate, aurothioglucose, aurothiomalate, auronofin, D-penicillamine, azathioprine, cyclophosphamide, cyclosporin A, FK506, and rapamycin. Another treatment regime entails the administration of at least two of these

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immunosuppressive agents. A further treatment regime entails administering an immunosuppressive agent in combination with at least one agent selected from the group consisting of a tricyclic antidepressant, a tetracyclic antidepressant, a Selective serotonin reuptake inhibitor (SSRI), a monoamine oxidase (MAO) inhibitor, caffeine, theophiline, theobromine, amphetamine, methylphenidate, dextroamphetamine, methamphetamine, pemoline, mazindol, modafinil, selegiline, ritanserin, viloxazine, CRL 40476, clomipramine, protriptyline, imipramine, desipramine, fluoxetine, paroxetine, sertraline, gammahydroxybutyrate (GHB), clonazepam, carbamazepine, and yohimbine. In some methods, the glucocorticoid is dexamethasone, methylprednisolone, prednisolone, or prednisone. In some such methods, the glucocorticoid compound is administered in combination with a therapeutically effective amount of a nonsteroidal anti-inflammatory agent. In some such methods, the nonsteroidal anti-inflammatory agent is an aspirin compound (acetylsalicylate), a non-aspirin salicylate, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, naproxen, naproxen sodium, phenylbutazone, sulindac, or tometin. In some methods, the glucocorticoid compound is administered in combination with a therapeutically effective amount of an agent selected from the group consisting of hydroxychloroquine, sulfasalazine, methotrexate, aurothioglucose, aurothiomalate, auronofin, D-penicillamine, azathioprine, cyclophosphamide, cyclosporin A, FK506, and rapamycin. In some methods the therapeutic agent is selected from the group consisting of: an anti-inflammatory cytokine, an anti-TNF- $\alpha$  antibody, a COX-1 inhibitor, a COX-2 inhibitor, an iNOS inhibitor, an nNOS inhibitor, and an antioxidant.

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The immunosuppressive agent is typically administered by intravenous infusion, transdermal delivery, intramuscular delivery, subcutaneous delivery, intracerebralventricular delivery, oral delivery, or by inhalation."

In col. 10 lines 12-50, Siegel et al. teach suitable treatment agents as: "...treatment agents of the present invention include immunosuppressive agents. Immunosuppressive agents are agents capable of suppressing immune responses. These agents include cytotoxic drugs, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), specific T-lymphocyte immunosuppressants, and antibodies or fragments thereof (see Physicians' Desk Reference, 53<sup>rd</sup> edition, Medical Economics Company Inc., Montvale, N.J. (1999); this reference and all references cited therein are herein incorporated by reference).

Cytotoxic or antimetabolic drugs include hydroxychloroquine, sulfasalazine, methotrexate, aurothioglucose, aurothiomalate, auranofin, D-penicillamine, azathioprine, and cyclophosphamide.

Glucocorticoids include dexamethasone, methylprednisolone, prednisolone, and prednisone.

NSAIDs include aspirin compounds (acetylsalicylates), non-aspirin salicylates, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, naproxen, naproxen sodium, phenylbutazone, sulindac, and tometin.

Specific T-lymphocyte immunosuppressants include cyclosporin A, FK506, and rapamycin.

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Treatment agents also can include other agents such as tricyclic antidepressants, tetracyclic antidepressants, SSRIs, monoamine oxidase (MAO) inhibitors, caffeine, theophylline, theobromine, amphetamine, methylphenidate, dextroamphetamine, methamphetamine, pemoline, mazindol, modafinil, selegiline, ritanserin, viloxazine, CRL 40476, clomipramine, protriptyline, imipramine, desipramine, fluoxetine, paroxetine, sertraline, gammahydroxybutyrate (GHB), clonazepam, carbamazepine, and yohimbine.

Other treatment agents include anti-inflammatory cytokines, anti-TNF- $\alpha$ -inverted, antibodies, COX-1 inhibitors, COX-2 inhibitors, iNOS inhibitors, nNOS inhibitors, and antioxidants."

In col. 12 line 5 to col. 13 line 11, Siegel et al. teach combination therapies such as: "...therapeutic agents described above can be used alone or in combinations with each other (see, e.g., Aldrich, M., Sleep Medicine, Oxford University Press, New York, N.Y.U.S.A. 1999 and Robinson, A. and Guilleminault, C. "Narcolepsy," in Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects, Chokroverty, S. (ed.) (Butterworth Heinemann Boston, Mass. U.S.A. 1999), pp 427-440; these references and the references cited therein are herein incorporated by reference).

Combination therapy includes administration of a single pharmaceutical dosage formulation which contains an immunosuppressive agent and one or more additional active agents, as well as administration of an immunosuppressive agent and each active agent in its own separate pharmaceutical dosage formulation. For example, a glucocorticoid (e.g., dexamethasone, methylprednisolone, prednisolone, or prednisone)

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and azathioprine can be administered to the human subject together in a single oral dosage composition, such as a tablet or capsule, or each agent can be administered in separate oral dosage formulations. Where separate dosage formulations are used, an immunosuppressive agent and one or more additional active agents can be administered at essentially the same time (i.e., concurrently), or at separately staggered times (i.e., sequentially). Combination therapy includes all these regimens.

There can be many advantages to combining two therapeutic agents into one regime. For example, if one combines prednisone and azathioprine, prednisone acts within hours or days whereas azathioprine can take up to a year to bring about an effect. In addition, different therapeutic agents can suppress immune function in different ways which can be necessary for the overall desired immunosuppressive effects. The addition of one treatment agent to another effective regime can also significantly increase the effectiveness of the treatment regime. An example of combination therapy that can be administered to a mammal susceptible to or suffering from narcolepsy to prevent, reduce, arrest, or reverse the development of narcoleptic symptoms comprises administering at least two of the following immunosuppressive agents: an NSAID, a glucocorticoid, hydroxychloroquine, sulfasalazine, methotrexate, aurothioglucose, aurothiomalate, auranofin, D- penicillamine, azathioprine, cyclophosphamide, cyclosporin A, FK506, or rapamycin.

Another example of combination therapy is treating narcolepsy in a mammal susceptible to or suffering from narcolepsy with a therapeutically effective amount of a glucocorticoid compound used in combination with, for example, a non-steroidal anti-

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inflammatory compound, hydroxychloroquine, sulfasalazine, methotrexate, aurothioglucose, aurothiomalate, auranofin; D-penicillamine, azathioprine, cyclophosphamide, cyclosporin A, FK506, or rapamycin. The immunosuppressive agents can also be effectively used in combination with, for example, antibodies to a cytokine or cytokine receptor, an anti-TNF- $\alpha$ -inverted, antibody, a COX-1 inhibitor, a COX-2 inhibitor, an iNOS inhibitor, and an antioxidant.

Another regime combines an immunosuppressive agent with at least one of the following active agents: a CNS stimulant and/or an anticonvulsant compound (e.g., caffeine, theophylline, theobromine, amphetamine, methylphenidate, dextroamphetamine, methamphetamine, pemoline, mazindol, modafinil, selegiline, ritanserin, viloxazine, CRL 40476, clomipramine, protriptyline, imipramine, desipramine, fluoxetine, paroxetine, sertraline, gamma-hydroxybutyrate (GHB), clonazepam, carbamazepine, or yohimbine). Other central nervous system stimulants or anticonvulsant compounds can include tricyclic or tetracyclic antidepressants, selective serotonin reuptake inhibitors (SSRI) and monoamine oxidase (MAOs) inhibitors." In col. 14 lines 19-32, Siegel et al. teach "The immunosuppressive agents and other active agents can be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration. The immunosuppressive agents and other active agents can be can also be formulated as sustained release dosage forms and the like.

Administration of the compounds can be achieved in various ways, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, transdermal, intratracheal, and

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intramuscular administration. Moreover, the compound can be administered in a local rather than systemic manner, in a depot or sustained release formulation. In addition, the compounds can be administered in a liposome."

Siegel et al. teach, in col. 17 lines 30-52, that "The invention further provides kits comprising an immunosuppressive agent which includes at least one of the following: a nonsteroidal anti-inflammatory, a glucocorticoid, hydroxychloroquine, sulfasalazine, methotrexate, aurothioglucose, aurothiomalate, auronofin, D-penicillamine, azathioprine, cyclophosphamide, cyclosporin A, FK506, or rapamycin. Optional additional components of the kit include, for example, other active compounds, in combination with at least one of the following active agents such as, but not limited to, a CNS stimulant and/or an anticonvulsant compound (e.g., caffeine, theophylline, theobromine, amphetamine, methylphenidate, dextroamphetamine, methamphetamine, pemoline, mazindol, modafinil, selegiline, ritanserin, viloxazine, CRL 40476, clomipramine, protriptyline, imipramine, desipramine, fluoxetine, paroxetine, sertraline, gammahydroxybutyrate (GHB), clonazepam, carbamazepine, or yohimbine). Other CNS stimulants or anticonvulsant compounds can include tricyclic or tetracyclic antidepressants, SSRI and MAO inhibitors. Usually, the kit also contains instructions for carrying out the methods."

Claims 10 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al. as applied to claims 1-9, 11-12, 15, 20-21, 46-48, 58-59, 60-63, 66, and 73-76 above, and further in view of The Merck Index monographs numbers 04972

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and 03712.

Seigel et al. is as taught above.

Seigel et al. while teaching the use of anti-inflammatory cytokines, anti-TNF $\alpha$  antibodies, COX-1 inhibitors, COX-2 inhibitors iNOS inhibitors, nNOS inhibitors and antioxidants does not explicitly teach infliximab and/or etanercept etc...

The Merck Index teaches in monograph 04972 that infliximab is a chimeric monoclonal antibody that binds and neutralizes soluble TNF $\alpha$ . It also teaches it has use as an anti-inflammatory.

The Merck Index teaches in monograph 03712 that etanercept is a recombinant protein consisting of the human soluble TNF receptor p75 linked to the Fc portion of human immunoglobulin G1 and that it inhibits the biological effects of TNF. It is taught also to be useful as an anti-inflammatory and an anti-psoriatic.

It would have been obvious to one of ordinary skill at the time of the invention to use etanercept and/or infliximab as the anti-inflammatory cytokines and/or anti-TNF $\alpha$  antibodies of Seigel et al. as etanercept and infliximab are such compounds respectively.

Claims 13-14, 16-18, 64-65 and 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al. (US Patent No. 6204245B1) as applied to claims 1-9, 11-12, 15, 20-21, 46-48, 58-59, 60-63, 66, and 73-76 above, in view of Linden et al. (Psoriasis: Current perspectives with an Emphasis on Treatment, The American Journal of Medicine, December 1999, vol. 107, pp. 595-605), in view of Guenther (ABSTRACT-



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Tazarotene combinatin treatments in psoriasis, J. Am. Acad. Dermatol., August 2000, vol. 43, pp. \$36-42) and further in view of Mitra (Role of anti-depressant fluoxetine in the puva treatment of psoriasis vulgaris, Indian Journal of Dermatology, Venereologyand Leprology, 2001, vol. 67, pp. 292-293).

Seigel et al. is as set forth above.

Seigel does not teach the use of anticholinergic compounds (such as ipratropium or tiotropim), beta receptor agonists (such as ibuterol sulfate, epinephrine, isoproteronol etc...), vitamin D analogs (such as calcipotriene or calcipotriol), psoralens (such as methoxsalen) or retinoids (such as acitretin or tazoretene) in combination with a SSRI and a corticosteroid (or glucocorticosteroid).

Linden et al. teach, in the abstract, that first line treatments for psoriasis include corticosteroids, calcipotriene and tazarotene. Additional treatments include phototherapy with ultraviolet B or photochemistry with psoralens plus ultraviolet A (PUVA), and systemic treatments including methotixate, acitretin or cyclosporin. On page 599-Table 2, Linden et al. disclose a list of corticosteroids useful in the treatment of psoriasis ranked by potency (the list includes hydrocortisone, dexamethasone, prednisolone, triamcinolone, betamethasone, etc... On page 603, Linden et al. teach that combination therapy wherein agents may be used sequentially or concomitantly with other agents is prudent to prevent side effects.

Guenther teaches, in the abstract, combination regimens comprisng tazarotene, calcipotriene, a mid-potency or high-potency steroid, UVB phototherapy and PUVA

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show enhanced efficacy and tolerability.

Mitra teaches, in the abstract, that the severity of psoriasis vulgaris (psoriasis) is modified by psychological stress. In a trial of ten patients given fluoxetine (to control stress) along with PUVA treatment for psoriasis showed better response and quicker remission than the control group.

The examiner respectfully points out the following from MPEP 2144.06:

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980). As all of the compounds have been individually shown to be utilized and effective in the treatment of psoriasis, and as all the references demonstrate combinations of the various compounds in a variety of formulations, the combination of all/or any of the claimed compounds is rendered obvious by the prior art. One would have been motivated to perform such combinations in expectation of achieving better treatments for psoriasis.

Claims 13-14 and 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al. (US Patent No. 6204245B1) as applied to claims 1-9, 11-12, 15, 20-21,46-48, 58-59, 60-63, 66, and 73-76 above, in view of Ahmed (US Patent No. 6281248) and further in view of The Merck Manual Section 4-Chapter 44-

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Asthma.

Siegel et al. is as set forth above.

Siegel et al. does not teach the use of beta receptor agonists (such as ibutanol sulfate, epinephrine, isoproterenol etc...) in combination with a SSRI and a corticosteroid (or glucocorticosteroid).

Ahmed teaches, in the abstract, a method of treating asthma by administration of a composition comprising a selective serotonin reuptake inhibitor (such as sertraline HCl). In col. 1 lines 10-60, Ahmed discloses that sympathomimetic drugs, such as epinephrine, isoproterenol and terbutaline, xanthine drugs and corticosteroid drugs have all been used to treat bronchial asthma.

The Merck Manual teaches, on pages 6-7, that drugs useful in treating/preventing asthma include beta adrenergic agonists such as epinephrine and albuterol and corticosteroids with a combination of a beta adrenergic agent and a corticosteroid giving better results than either individually. Additional drugs useful in the treatment of asthma include theophylline, ipratropium, beclomethasone, budesonide, triamcinolone etc...

The examiner respectfully points out the following from MPEP 2144.06:

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846,

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850,205 USPQ 1069, 1072 (CCPA 1980). As all of the compounds have been individually shown to be utilized and effective in the treatment of asthma, and as all the references demonstrate combinations of the various compounds in a variety of formulations, the combination of all/or any of the claimed compounds is rendered obvious by the prior art. One would have been motivated to perform such combinations in expectation of achieving better treatments for asthma.

### ***Conclusion***

Claims 1-21, 46-48, 58-69, and 73-76 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617

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